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Study of Herbal Anti-Cancer Agents

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ABSTRACT

Nowadays, cancer is one of the deadliest diseases in the world, which has been estimated to cause 9.9 million deaths in 2020. Conventional treatments for cancer commonly involve monochemotherapy or a combination of radiotherapy and mono-chemotherapy. However, the negative side effects of these approaches have been extensively reported and have prompted the search of new therapeutic drugs. In this context, scientific community started to look for innovative sources of anticancer compounds in natural sources, including traditional plants. Currently, numerous studies have evaluated the anticancer properties of natural compounds derived from plants, both in vitro and in vivo.

In pre-clinical stages, some promising compounds could be mentioned, such as the sulforaphane or different phenolic compounds. On the other hand, some phytochemicals obtained positive results in clinical stages and were further approved for cancer treatment, such as vinca alkaloids or the paclitaxel. Nevertheless, these compounds are not exempt of limitations, such as low solubility, restricted effect on their own, negative side-effects, etc. This review aims to compile the information about the current phytochemicals used for cancer treatment and also promising candidates, main action mechanisms and also reported limitations. In this sense, some strategies to face the limitations have been considered, such as nano-based formulations to improve solubility or chemical modification to reduce toxicity. In conclusion, although more research is still necessary to develop more efficient and safe phytochemical drugs, more of these compounds might be used in future cancer therapies.

KEYWORDS

Natural compounds; traditional plants; anticancer; clinical/pre-clinical studies; challenges, Vinca, Vincrystine, Vinblastine.

INTRODUCTION

Cancer is one of the deadliest diseases globally and especially in western countries. According to the International Cancer Observatory, roughly 9.9 million people have died in 2020 as a result of developing cancer. Cancer is a complex disease, generally defined as an uncontrolled proliferation and development of cells in tissues forming an amalgamation and microenvironment (tumor) that may potentially expand to a whole organ or systemically to other tissues (metastasis). This abnormal cell behavior may be the result of hereditary

genetics, or an epigenetic-driven alteration of key genes (oncogenes) related to the cell cycle and regulation of cell death (apoptosis). Cancerous cells are also characterized by dysregulation of programmed apoptosis and aberrant behavior of microtubules, as they are involved in the mitotic process. The World Health Organization identifies as main causes behind the development of cancer random somatic mutations, ionizing radiation, reactive oxidative species as well as several chemical and biological agents.

Except for random mutations, these are widely recognized exogenous carcinogens. Ionizing radiation is able to disrupt the hydrogen bonds between nucleic acids as well as altering their chemical conformation, which may yield alterations in normal DNA expression regulation. Infectious diseases caused by bacteria, fungi or viruses have also been significantly correlated with developing cancer afterward in the same affected tissues.

Cancer is truly a general term that describe a huge assembly of identified diseases. Each instance of cancer is one of a kind, with its own set of hereditary progressions and development lands. A few cancers develop rapidly while others can take years to end up hazardous to the patient. The numerous distinctions between instances of cancer, even of the same organ (i.e. distinctive instances of bosom cancer), is one of the fundamental explanations that medication is so challenging.

DEFINITIONS

CANCER - Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs.

ANTI-CANCER - Anticancer drug, also called antineoplastic drug, any drug that is effective in the treatment of malignant, or cancerous, disease. There are several major classes of anticancer drugs; these include alkylating agents, antimetabolites, natural products, and hormones.

Example

There are four classes of plant-derived anticancer agents in the market today, the vinca alkaloids (vinblastine, vincristine and vindesine), the epipodophyllotoxins (etoposide and teniposide), the taxanes (paclitaxel and docetaxel) and the camptothecin derivatives (camptotecin and irinotecan).

SOME BASIC FACTS ABOUT CANCER

- Cancer cells have lost the normal regulatory mechanisms that control cell growth and multiplication.
- Cancer cell have lost their ability to differentiate (that means to specialize)
- **Benign** cancer cell stay at the same place

- **Malignant** cancer cells invade new tissues to set up secondary tumors, a process known as **metastasis**
- Chemicals causing cancer are called **mutagens.**
- Cancer can be caused by chemicals, life style (smoking), and viruses.
- Genes that are related to cause cancer are called **oncogenes**.
  Genes that become oncogenic upon mutation are called **proto-oncogenes**.

MECHANISM OF ACTION

- Contain planar aromatic or heteroaromatic ring systems.
- Planar systems slip between the layers of nucleic acid pairs and disrupt the shape of the helix.
- Preference is often shown for the minor or major groove.
- Intercalation prevents replication and transcription.
- Intercalation inhibits topoisomerase II (an enzyme that relieves the strain in the DNA helix by temporarily cleaving the DNA chain and crossing an intact strand through the broken strand.

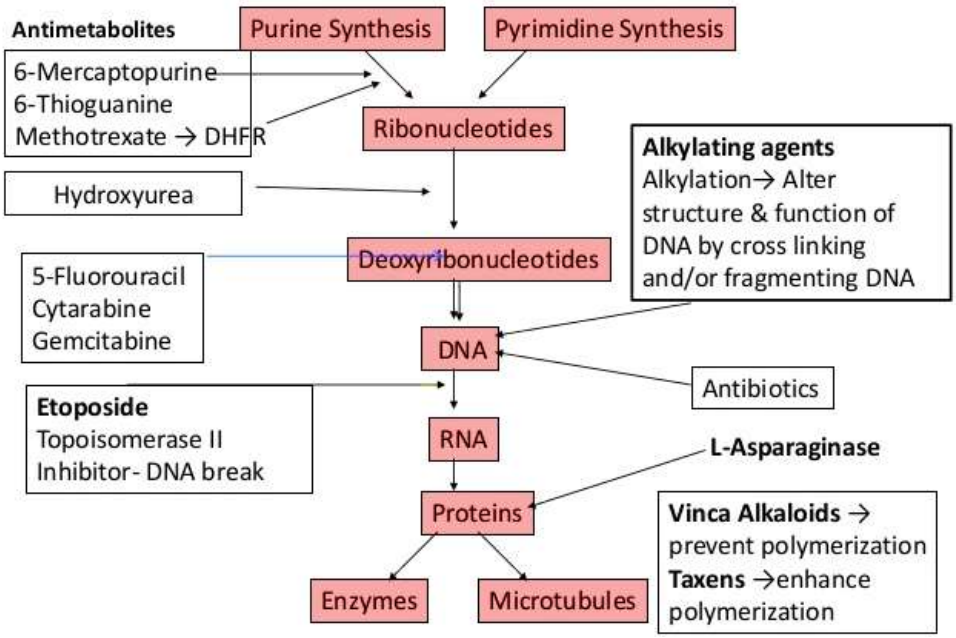

Fig. Mechanism of Action of Some Anti-Cancer Agents

Uses:

Chemotherapy, also known as chemo or anticancer medication, is medication that is used to destroy, kill, shrink, or slow the growth of cancer cells.

- Boost the immune system
- Ease cancer symptoms
- Reduce treatment side effects
- Slow cancer spreading (metastasis)
- Attack cancer cells

Advantages of Herbal Anticancer Agents:

1. Herbal Anticancer agents have less side effects.
2. They have less chances of Toxicity.
3. They are preferred for Chronic Treatment.
4. Source of Herbal anticancer agents have potent activity like Vinca (Vincristine & Vinblastine)
5. Herbal Medicines may use to develop new drugs.

Disadvantages of Herbal Anticancer Agents:

1. Herbal drugs have less amount of Active ingredient.
2. Herbal drug may contain toxic factors or heavy metal or react harmful with other drug.
3. Some herbal medicines may cause kidney failure and liver damage.

Some Drugs used as Herbal Anticancer Agents:

1. **Angelica sinensis:**

Commonly known as dong quai or female ginseng, is an herb belonging to the family Apiaceae, indigenous to China. Angelica sinensis grows in cool high altitude mountains in China, Japan, and Korea. The yellowish brown root of the plant is harvested in the fall and is a well-known Chinese medicine which has been used for thousands of years.

Growing environment:

Angelica is hardy to -5 C and can be cultivated at an altitude of 1500-3000m. Seedlings need to be kept out of direct sunlight, but the mature plant can withstand it. Angelica requires deep moist fertile soil and is perennial if prevented from going to seed.

Traditional Chinese medicine:

The dried root of A. sinensis – commonly known as Chinese angelica (Chinese: 當歸; pinyin: dāngguī; Pe̍h-ōe-jī: tong-kui) – is widely used in traditional Chinese medicine, although there is insufficient evidence that it has any medicinal effect.

Adverse effects:

There is evidence that A. sinensis may affect the muscles of the uterus. Women who are pregnant or planning on becoming pregnant should not use A. sinensis, because it may induce a miscarriage. Taking A. sinensis can cause skin to become extra sensitive to the sun, leading to a greater risk for skin cancer.

Drug Interaction:

A sinensis may increase the anticoagulant effects of the drug warfarin (as it contains coumarins) and consequently increase the risk of bleeding.

Due to the antiplatelet and anticoagulant effects of A. sinensis, it should be taken with caution with herbs or supplements (such as ginkgo, garlic, and ginger) that may slow blood clotting to reduce the possible risk of bleeding and bruising.

Chemistry:

The plant's chemical constituents include phytosterols, polysaccharides, ligustilide, butylphthalide, cnidilide, isoenidilide, p-cymene, ferulate, and flavonoids. When isolated from the plant, one of the chemicals, angelica polysaccharide sulfate, has in vitro antioxidant activity.

2. Burdock root:

Burdock is a plant that is found all over the world. Burdock root is sometimes used as food. The root, leaf, and seed are used as medicine. Arctium is a genus of biennial plants commonly known as burdock, family Asteraceae. Native to Europe and Asia, several species have been widely introduced worldwide.

Description of plant:

Plants of the genus Arctium have dark green leaves that can grow up to 70 cm (28 in) long. They are generally large, coarse and ovate, with the lower ones being heart-shaped. They are woolly underneath. The leafstalks are generally hollow. Arctium species generally flower from July through to October. Burdock flowers provide essential pollen and nectar for honeybees around August when clover is on the wane and before the goldenrod starts to bloom.

The roots of burdock, among other plants, are eaten by the larva of the ghost moth (Hepialus humuli). The plant is used as a food plant by other Lepidoptera including brown-tail, Coleophora paripennella, Coleophora peribenanderi, the Gothic, lime-speck pug and scalloped hazel.

The prickly heads of these plants (burrs) are noted for easily catching on to fur and clothing. In England, some birdwatchers have reported that birds have become entangled in the burrs leading to a slow death, as they are unable to free themselves. Burdock's clinging properties, in addition to thus providing an excellent mechanism for seed dispersal, led to the invention of the hook and loop fastener.

A large number of species have been placed in genus Arctium at one time or another, but most of them are now classified in the related genus Cousinia. The precise limits between Arctium and Cousinia are hard to define; there is an exact correlation between their molecular phylogeny. The burdocks are sometimes confused with the cockleburs (genus Xanthium) and rhubarb (genus Rheum).

Chemical Constituents:

Fresh burdock root is chemically composed of ca. 70 % water, 2.8 % protein, 25 % carbohydrate and 0.6 % ash. Burdock root contains mostly inulin, amino acids, sulphur-acetylene class, multi-polyacetylenes, poly- phenols and volatile oil, among others.

Adverse Effects:

a) If you're taking burdock supplements, take only in moderation. More research is needed to determine the safety of the supplement.

b) Burdock is considered to be safe to eat, but you should only buy it from reputable sellers and should never collect it in the wild. The burdock plant resembles belladonna nightshade plants, which are highly toxic. They often grow together.

c) Burdock root is a natural diuretic, so you shouldn't take it if you're dehydrated. You also shouldn't take it if you're also taking other diuretics or water pills, as it can increase dehydration.

d) If you're allergic to chrysanthemums or daisies, you may be at an increased risk of having an allergic reaction to burdock root and should avoid it.

e) Pregnant women or women trying to become pregnant shouldn't take burdock root or supplements.

Drug Interaction:

Burdock might slow blood clotting. Taking burdock along with medications that also slow clotting might increase the chances of bruising and bleeding.

Some medications that slow blood clotting include aspirin, clopidogrel (Plavix), diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, warfarin (Coumadin), and others.

3. Essaic tea:

Essiac is an herbal tea promoted as an alternative treatment for cancer and other illnesses. There is no evidence it is beneficial to health. In a number of studies Essiac either showed no action against cancer cells, or actually increased the rate of cancer growth.The Essiac variation, "Flor Essence" in particular has shown evidence of being harmful, with laboratory tests demonstrating that it increased the growth of breast cancer cells.

Side effects: Essiac may cause headache, nausea, diarrhea or constipation, vomiting, low blood sugar, liver damage, and kidney damage. Allergic rashes are possible. Rarely, serious allergic reactions have been reported."

Effectiveness: Essiac's purported effect on cancer has been reviewed by several major medical and scientific bodies, including the U.S. Food and Drug Administration (FDA), the National Cancer Institute, and the American Cancer Society. The American Cancer Society states that "Reviews of medical records of people who have been treated with Essiac do not support claims that this product helps people with cancer live longer or that it relieves their symptoms." The NCI states "Essiac and Flor Essence have not reported clear evidence of an anticancer effect"

What is essiacs tea?

- Essiac tea is a popular herbal tea touted for its purported anticancer properties.
- In the 1920s, Canadian nurse Rene Caisse promoted Essiac tea as a natural cancer treatment, claiming that it was given to her by a patient who originally received it from an Ontario Ojibwa medicine man.
- Though the tea is still said to be a Native American natural remedy, evidence to back up this claim is limited.
- Essiac tea is a blend of different herbs, including burdock root, slippery elm, sheep sorrel and Indian rhubarb.
- In addition to its purported anticancer properties, Essiac tea is also believed to enhance detoxification, boost immune function and reduce inflammation.

4. Hypericum:

Hypericum is a genus of flowering plants in the family Hypericaceae (formerly considered a subfamily of Clusiaceae). The genus has a nearly worldwide distribution, missing only from tropical lowlands, deserts and Polar Regions Many Hypericum species are regarded as invasive species and noxious weeds. All members of the genus may be referred to as St. John's wort, and some are known as goatweed. The white or pink flowered marsh St. John's worts of North American and eastern Asia are now separated into the genus.

Description:

Hypericum species are quite variable in habit, occurring as trees, shrubs, annuals, and perennials. Trees in the sense of single stemmed woody plants are rare, as most woody species have multiple stems arising from a single base. Shrubs have erect or spreading stems but never root from nodes that touch the ground. However, perennial herbs tend to root from these horizontal nodes, especially those that occur in wet habitats. Annual herbs tend to have taproots with a developed system of secondary hair roots. Many species of Hypericum are completely glabrous, others have simple uniseriate hairs, and some species have long, fine hairs.

Use in cancer:

Hypericin is known to generate a high yield of singlet oxygen and other reactive oxygen species that are associated with photo-oxidative cellular damage. The application of PDT with hypericin for the treatment of cancers such as recurrent mesothelioma and skin cancer has been validated in clinical trials**.**

5. Vinca:

Catharanthus roseus, commonly known as bright eyes, Cape periwinkle, graveyard plant, Madagascar periwinkle, old maid, pink periwinkle, rose periwinkle, is a species of flowering plant in the family Apocynaceae. It is native and endemic to Madagascar, but grown elsewhere as an ornamental and medicinal plant. It is a source of the drugs vincristine and vinblastine, used to treat cancer. It was formerly included in the genus Vinca as Vinca rosea.

Description:

Catharanthus roseus is an evergreen subshrub or herbaceous plant growing 1 m (39 in) tall. The leaves are oval to oblong, 2.5–9 cm (1.0–3.5 in) long and 1–3.5 cm (0.4–1.4 in) broad, glossy green, hairless, with a pale midrib and a short petiole 1–1.8 cm (0.4–0.7 in) long; they are arranged in opposite pairs. The flowers are white to dark pink with a darker red centre, with a basal tube 2.5–3 cm (1.0–1.2 in) long and a corolla 2–5 cm (0.8–2.0 in) diameter with five petal-like lobes. The fruit is a pair of follicles 2–4 cm (0.8–1.6 in) long and 3 mm (0.1 in) broad.

Use:

Vinblastine and vincristine, chemotherapy medications used to treat several types of cancers, are found in the plantand are biosynthesised from the coupling of the alkaloids catharanthine and vindoline. The newer semi-synthetic chemotherapeutic agent vinorelbine, used in the treatment of non-small-cell lung cancer, can be prepared either from vindoline and catharanthine or from the vinca alkaloid leurosine, in both cases via anhydrovinblastine. The insulin-stimulating vincoline has been isolated from the plant.

Mechanism of Action of Vinca:

Vinca cause cytotoxicity is due to their interactions with disruption of microtubule function and tubulin, especially of microtubules comprising the mitotic spindle fiber and causing metaphase arrest. They can perform some other biochemical response which can be effective or may not be effective on microtubules. Have some effect which do not interrupted the microtubule only after treatment of cells with clinically irrelevant doses of the vinca. Vinca and other anti-microtubule drug are also shows effect on both malignant cells and non-malignant cells in the non-mitotic cell cycle, because microtubules are involved in various nonmitotic functions.

Vinca are connected to binding sites of tubulin which is separate from the taxanes, colchicine, podophyllotoxin and guanosin-5'-triphosphate. Binding occur rapidly and can reverse too. Maintains the existence of vinca binding site / mole of tubulin dimer. 16-17 high affinity binding sites in each microtubule which is located at the end of per microtubule. The vinca bind at the binding site and interrupts microtubule congregations,but low drug concentration can be decreasing the rates of both growth and shortening at the assembly end of the microtubule that can cause produces a " kinetic cap "and suppresses function.The distributing effects of the vinca on microtubules dynamics, particularly at the ends of mitotic spindle, which causes metaphase arrest, occur at drug concentrations below those that decrease microtubule mass. The vinca and other microtubule distort agents have power to inhibit malignant angiogenesis in vitro.

Anticancer Property of Vinca:

The anticancer active ingredients Vinblastin and Vincristine are derived from the leaf and stem of vinca. They inhibit the growth of human tumors. Vinblastine is used experimental or treatment of neoplasmas and for Hodakins disease, choric carcinoma. Vincristine and anothers active ingredients are used for leukemia in children.

6. Andrographis paniculata:

It is commonly known as kalmegha in Hindi and king of bitters in English and belongs to Acanthaceae family. It is found in the India and Sri Lanka. Generally roots and leaves are used for the medicinal purpose; extract of this plant contains flavonoids, stigmasterols and diterpenes. The main compound of this plant is the andrographolide which is a diterpene, it is colorless crystilline in nature and bitter in taste. Leaves contains highest amount of andrographolide (approxemately2.25%) while the seeds contains very low amount of this compound. Studies in mice have shown that Andrographis paniculata stimulates immune system and activates both the antigen specific and nonspecific immune response. Due to this ability, plant is effective against various oncogenic and infectious agents.

Andrographolide shows cytotoxic effects against various cancer cells. It shows cytotoxic effect against breast cancer cells (MCF-7), P388 lymphocytic cells and colon cancer cells (HCT-116). Andrographolide shows inhibition of growth in colon cancer cell line HT 29 and enhance growth and division of human peripheral blood lymphocytes on mouse myeloid leukemia M1 cell lines.

Chemical Constituents:

Andrographolide exhibits multiple pharmacological properties and is a potential chemotherapeutic agent. Andrographolide contains an α-alkylidene γ butyrolactone moiety and three hydroxyls at C-3, C-19 and C-14 responsible for the cytotoxic activities of andrographolide against many cancer cell lines.

7. Azadirachta indica:

It belongs to the Meliacear family and commonly known as neem or the Indian liliac. It is a tree native to the Indian subcontinent and belongs to the family Meliaceae. The lead anticancer component in neem is limonoidsincluding azadirachtin and nimbolide that induce apoptosis of tumor cells by targeting different cell signaling pathways. There are various theories of cell apoptosis by neem such as activation of proapoptotic proteins like Bax and Bak to permeabilize mitochondria and inhibiting the activity of Bcl-2 and mutant p53 in the 7, 12-dimethylbenz (a) anthracene (DMBA)-induced cancer cells. However there is no evidence on the culminating reasons of neem induced apoptosis. A study on limonoids shows that neem exhibits caspase dependent cell apoptosis and release reactive oxygen species to inhibit metastasis. The neem leaf glycoprotein regulates the activity of M2 macrophages, by

converting it to M1 phenotypes in tumor core. This restricts the growth of melanoma and prevents the relapse of tumor by disseminating tumor mass. The vital properties of neem components on tumor cells include enhancing immune response, inhibiting cell proliferation, inducing cell apoptosis, suppression of cancer angiogenesis, and restoration of cellular reduction/oxidation (redox) balance. Neem extracts enhance the efficacy of certain chemotherapeutic drugs and sensitize malignant cells to immunotherapy and radiotherapy.

Azadirachta Used as Anticancer:

Azadirachta indica (Neem) is a medicinal plant of Indian origin, a tree with more of 140 isolated compounds and at least 35 biologically active principles that have shown an important influence as tumor suppressors by interfering with the **carcinogenesis process**.

8. Boesenbergia Pandurata:

It belongs to the Zingiberaceae family and it's a perennial herb. It is native to the South east Asia and commonly called as finger root or Chinese ginger The active compounds in B. pandurata are boesenbergin, cardamonin, pinostrobin, pinocembrin, panduratin A and 4-hydroxypanduratin A. These compounds act as antioxidant, antibacterial, antifungal, anti-inflammatory, antitumor and anti-tuberculosis agents. A cyclohexenylchalcone derivative, Panduratin A, present in B. pandurate is shown to inhibit the growth and induce apoptosis of HT-29 colon cancer cells. A study reported that Panduratin A arrested the cancer cell lines A549 non-small cell lung cancer; PC3 and DU145 prostate cancer cells and MCF-7 breast cancer cells and illustrated proapoptotic activities. Mohd Isa et al. [10] investigated the anticancer role of Boesenbergin a (BA) isolated from Boesenbergia rotunda in human non-small cell lung cancer (A549) cells. BA arrested the cell cycle by accumulating the cells in sub G1 phase. BA stimulated the expression of pro-apoptotic Bcl-2 family members, caspase 3/7, 9 and 8.The study thus concludes that BA could be a promising agent for the treatment of lung cancer.

Boesenbergia pandurata Used as Anticancer:

Pandurata showed **strong inhibitory effects on** the growth of cancer cells, similar to ethanolic extract of Curcuma longa. C. longa and its bioactive compound, curcumin, have shown potential anticancer activity in in vitro and in vivo studies and have undergone clinical trials.

9. Boswellia Serrata:

It is belongs to Bursersceae family and found in India North Africa, and Middle East. It is commonly known as olibanum or Indian olibanum. It contains various compounds like terpenoids, oils and sugars. The main constitute of this plant is Boswellic acid. Gummy exudates of this plant are associated with the therapeutic effect which includes anti-arthriticc, astringent, stimulant and anti-septic effects. Acetyl-11-keto-β-boswellic acid which is an active compound of this plant shows potential activity to inhibit tumor angiogenesis through the vascular endothelial growth factor signaling. Studies showed that treatment with acetyl-11-keto-β-boswellic acid (dose-10mg/kg) suppress tumor growth in xenograft mice with human prostate. This shows the anti-tumor activity of this plant.

Boswellia serrata oleo gum resin has long been used in Ayurvedic and traditional Chinese medicine to alleviate a variety of health problems such as inflammatory and arthritic diseases. The current study aimed to identify and explore the in vitro anticancer effect of B.

Boswellia as Anticancer:

Boswellic acids act in a number of **ways that may inhibit cancer growth**. Boswellic acids have been shown to prevent certain enzymes from negatively affecting DNA. Studies have also found that boswellia may fight advanced breast cancer cells, and it may limit the spread of malignant leukemia and brain tumor cells.

10. Capparis spinose:

It belongs to the Capparaceaen family and an important culinary ingredient in Mediterranean and Middle Eastern cuisines. It is known as Himsra, Cabra in Sanskrit. Caper constitutes various volatile and nonvolatile compounds likeflavonol glycoside, rutinand 5-caffeoyl-quinic acid those are potent anti-cancer agents. A protein analogus to imidazoleglycerol phosphate synthase was purified from fresh Caper seeds that inhibited proliferation of hepatom0061 HepG2 cells, colon cancer HT29 cells and breast cancer MCF-7 cells. Essential oils and aqueous infusions extracted from Caper have shown significant inhibitory effect on HT-29 cell proliferation and on nuclear factor kB (NF-kB) activity in a dose dependent manner. Caper essential oil and aqueous infusion ceased the cells in G2/ M phase of cell cycle. A study has reported C. spinosa extract mediated apoptosis through permeabliztion of mitochondria and activation of Caspase 9 in SGC-7901 cells.

Uses of Capparis Spinosa:

Spinosa extract had high antioxidant activity and MTT assay indicated that C. spinosa extract effectively decreased the cancer cell lines. The quercetin in C. spinosa extract had **significant anti-tumor effects** and may be regarded as an ideal natural drug for cancer therapy.

Conclusion:

Why Herbal Medicines Superior then Modern Medicines ?

Natural products and traditional medicines are of great importance. Such forms of medicine as traditional Chinese medicine, Ayurveda, Kampo, traditional Korean medicine, and Unani have been practiced in some areas of the world and have blossomed into orderly-regulated systems of medicine. This study aims to review the literature on the relationship among natural products, traditional medicines, and modern medicine, and to explore the possible concepts and methodologies from natural products and traditional medicines to further develop drug discovery. The unique characteristics of theory, application, current role or status, and modern research of eight kinds of traditional medicine systems are summarized in this study. Although only a tiny fraction of the existing plant species have been scientifically researched for bioactivities since 1805, when the first pharmacologically-active compound morphine was isolated from opium, natural products and traditional medicines have already made fruitful contributions for modern medicine. When used to develop new drugs, natural products and traditional medicines have their incomparable advantages, such as abundant clinical experiences, and their unique diversity of chemical structures and biological activities.

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